ROLE OF ACARBOSE IN GLYCEMIC CONTROL

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(PHARMACY PRACTICE)

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DECLARATION

I do hereby declare that the dissertation work entitled **"ROLE OF ACARBOSE IN GLYCEMIC CONTROL"** submitted to the Tamil Nadu Dr.M.G.R. Medical University, Chennai ,in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmacy Practice,** was done under the guidance of **Mrs K Geetha, M pharm., (Ph.D.,)** at the department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, during the academic year 2011-2012

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EVALUATION CERTIFICATE

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Convener of Examination

Dedicated to God Almighty

&

My Parents

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Sheena Marin Thomas

Abbreviations

ABBREVIATIONS

ADA	-	American Diabetes Association
UKPDS	-	United Kingdom Prospective Diabetes Study
DCCT	-	Diabetes Control And Complications Trial
DM	-	Diabetes Mellitus
BP	-	Blood Pressure
PVD	-	Peripheral vascular disease
NIDDM	-	Non Insulin Dependent Diabetes Mellitus
DIS	-	Diabetes Intervention Study
FBS	-	Fasting Blood Sugar
PPBS	-	Post Prandial Blood Sugar
HbA_{1C}	-	Glycosylated Haemoglobin
IGT	-	Impaired Glucose Tolerance
MI	-	Myocardial Infarction
HDL	-	High Density Lipoprotein
LADA	-	Latent Autoimmune Diabetes in Adults
BMI	-	Body Mass Index
mg	-	milligram
dl	-	decilitre
OHA	-	Oral Hypoglycemic Agent
AGIs	-	Alpha Glucosidase Inhibitors
S.D	-	Standard Deviation

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ABSTRACT

The prevalence of Type II diabetes is rising rapidly worldwide with Africa and Asia having the greatest potential increases. Acarbose an α-glucosidase inhibitor, acts specifically at the level of postprandial glucose excursion. Its used in combination with oral hypoglycemics and insulin. The aim of the study was to evaluate the efficacy of Acarbose in improving the glycemic control in Type II diabetic patients. This prospective study conducted on 74 Type II Diabetic patients included both male and female patients having HbA_{1C} value above 6.5%. Among 74 patients 40 patients were on Acarbose therapy and 34 patients were in another group taking oral hypoglycemics other than Acarbose. Its efficacy in obese and non obese type II diabetic patients and the percentage reduction in blood glucose values were done. Its effect in reducing the PPBS and HbA_{1C} values were found to be higher in obese patients than non obese patients. The p value of PPBS and HbA_{1C} in obese patients were found to be ($p=0.0006$) and ($p<0.0001$). Similarly patients on Acarbose therapy showed a significant reduction in blood glucose values than patients on oral hypoglycemic agents alone. It is associated with improvement in glycemic parameters and was safe and well tolerated. After a period of three months when the patients came for the first review it has been found that patients taking Acarbose with oral hypoglycemic agents and Insulin therapy showed 18.8% reduction in FBS, 16.82% reduction in PPBS and 17.92% reduction in HbA_{1C}. Thus it was concluded that Acarbose represents a new approach to the management of NIDDM, modulating gastrointestinal carbohydrate metabolism to control postprandial hyperglycemia and to maximize long-term glycemic control.

Introduction

INTRODUCTION

Diabetes mellitus is one of the most common endocrine disorders affecting almost 6% of the world's population, with the majority having Type II diabetes. The global prevalence of diabetes is estimated to rise substantially, with an accompanying increase in diabetes-related morbidity and mortality. It predisposes individuals to vascular, renal, ophthalmic and neurological complications and is a major risk factor for cardiovascular disease.[1] It is most commonly due to autoimmune Type I diabetes or to adult-onset Type II diabetes. Insufficiency of insulin affects the metabolism of carbohydrate, protein and fat which can cause a significant disturbance of water and electrolyte homeostasis[2]

Type I Diabetes Mellitus

It results from immune mediated destruction of the β cells of the pancreas which results in absolute insulin deficiency. About 5 to 10% of people with diabetes have type1 disease.[3] It usually occurs in children and adolescents but it can affect at any age. Younger individuals have a rapid rate of β-cell destruction and have ketoacidosis, for many years adults maintain sufficient insulin secretion to prevent ketoacidosis, which is often referred to as LADA[4]

Type II Diabetes Mellitus:

It is a chronic disease, resulting from interplay between genetic and environmental factors and characterised by hyperglycaemia. It is associated with the development of microvascular complications, such as retinopathy, neuropathy and nephropathy, and of macrovascular complications, which increase the risk of cardiovascular events.[5]

There is an abundance of evidence showing that good glycemic control reduces the risk of microvascular damage. Intensive glucose control significantly reduced the risk of microvascular complications.[6] Obesity is a disorder and it results from a complex interplay of environmental and genetic factors which is associated with significant morbidity and mortality. Thus the afflicted suffer emotional consequences from social stigmatization and consequently have an increased risk of many medical disorders.[7]

The prevalence and incidence of Type II diabetes is rising rapidly worldwide with Africa and Asia having the greatest potential increases. Lifestyle changes in Asia resulting from urbanization and industrial development have triggered epidemic rises in type 2 diabetes. The UK Prospective Diabetes Study has shown that intensive blood glucose control is essential for reducing the risk of developing diabetes sequelae .[8]

Type 1 treatment necessitates Insulin therapy. Treatment of Type II often necessitates use of multiple therapeutic agents including oral antihyperglycemics and insulin to obtain glycemic goals.[9] The different prevention strategies for type 2 DM are lifestyle changes, dietary restriction of fat, aerobic exercise and weight loss form the backbone of successful prevention.[10]

In addition, in the long term majority of patients need multiple therapies to attain these glycemic target levels. Even with Sulfonylurea and Metformin combination therapy, most patients end up with secondary failure and a third agent is needed to achieve HbA_{1C} target values.[11]. Results of recent evidence-based clinical studies, acarbose, indicate that an α- glucosidase inhibitor, has a beneficial effect on glycemic control without weight gain effect in Type II diabetes mellitus.[12]

The first step in evaluation of obesity is calculation of BMI. It is usually calculated by dividing weight (in kilograms) by square height (in meters). It correlates significantly with body fat, morbidity, and mortality and can be calculated quickly and easily.[7] Dietary measures, lifestyle changes, and oral therapy using Sulfonylureas, Biguanides or Insulin often do not achieve adequate results; monotherapy with antidiabetic agents, in particular, fails to control blood glucose levels satisfactorily in the long-term.[13] The pseudo-tetrasaccharide Acarbose delays the digestion of complex carbohydrates and disaccharides by competitive α-glucosidase inhibition at the ciliated border of the small intestine.[8] It has been estimated that 86% of those with type 2 diabetes are overweight or obese. It is associated with significantly worse cardiovascular risk factors in these patients.[14]

Persisting hyperglycemia has been linked to the development of diabetic complications and to the exaggeration of insulin resistance and impaired insulin secretion that characterizes the pathophysiology of non-insulin-dependent diabetes mellitus.[15] Diet therapy remains the cornerstone of the treatment strategies for non-insulin-dependent diabetes mellitus; it is intended to achieve and maintain ideal body weight[16]

The secondary complications of diabetes are highly correlated with long-term control of blood glucose levels. The findings of the Diabetes Control and Complications Trial (DCCT), performed by the American Diabetes Association, clearly demonstrate a close relationship between quality of glycemic control in insulin-dependent diabetes mellitus as indicated by HbA_{1C} levels, and the incidence of diabetes-specific complications.[17-18] In the 11-year follow-up of the diabetes intervention study (DIS) with newly detected NIDDM postprandial hyperglycemia was an independent risk

factor for both incidence of myocardial infarction and all-cause mortality. Perfect control of postprandial hyperglycemia, blood pressure, and triglycerides according to the target categories of the NIDDM study was associated with significantly fewer events.[1]

α-Glucosidase Inhibitors

α-Glucosidase inhibitors (AGIs) reduce intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of α-glucosidase in the intestinal brush border[20], Inhibition of this enzyme slows the absorption of carbohydrates; the postprandial rise in plasma glucose is blunted in both normal and diabetic subjects.[21] Mainly three AGIs exist such as Acarbose, Miglitol and Voglibose Among the inhibitors it has been shown that Acarbose could prevent or delay the development of IGT in Type 2 Diabetes. They usually have a decreasing effect on fasting and post load insulin levels compared to Sulphonyl Urea.[22]

Titrating the dose of drug slowly (25 mg) at the start of a meal for 4 to 8 weeks, followed by increases at 4- to 8-week intervals to a maximum of (75 mg) before each meal reduces gastrointestinal side effects.[23] It is most effective when given with a starchy, high-fiber diet with restricted amounts of glucose and sucrose. If hypoglycemia occurs when α-glucosidase inhibitors are used with insulin or an insulin secretagogue, glucose rather than sucrose, starch, or maltose should be administered.[21] They act by a reversible inhibition of alpha glucosidase which is an enzyme present in the brush border of small intestine. They delay the absorption of complex carbohydrates and thus inhibit post prandial glucose peaks band leads to decreased post prandial insulin levels[22]

AGIs are widely used in the treatment of patients with type 2 diabetes. It usually delay the absorption of carbohydrates from the small intestine and have a lowering effect on postprandial blood glucose and insulin levels. They have clear beneficial effects on glycemic control and postload insulin levels but not on plasma lipids.[24]

Acarbose

Acarbose is an α-glucosidase inhibitor, acts specifically at the level of postprandial glucose excursion. In patients with type 2 diabetes, Acarbose is used as monotherapy and in combination with oral glucose-lowering agents and insulin. It is associated with improvement in glycemic parameters, and was safe and well tolerated.[25]

It is a novel drug that attenuates postprandial hyperglycemia by delaying carbohydrate digestion, without causing major side effects. It initiate a cascade of events, leading to improved metabolic control. The drug smoothes the glycemic curve and causes a reduction in postprandial blood glucose levels and hyperinsulinemia, reducing hepatic triglyceride biosynthesis. It also probably inhibits the development of insulin resistance. [26]

It is an inhibitor of α-glucosidase and thus acts directly at the gastrointestinal level slowing down the intestinal absorption of glucose and reducing the rapid increase in glycemia induced by a meal rich in carbohydrates.[27] The degree of improvement of fasting and postprandial glycemia is confirmed by the significant reduction of HbA_{1C}. It is effective in reducing postprandial glycemia and glycosylated haemoglobin in patients normally treated with diet, with Sulphonyl Ureas, Metformin or Insulin.[28]

There is increasing epidemiological evidence for the association of PPBS levels and macrovascular complications in nondiabetic and diabetic individuals. A reduction of postprandial blood glucose levels by the Acarbose, delays glucose release from complex carbohydrates, and associated with a risk reduction of cardiovascular disease. Meta analysis of seven randomized, double-blind, placebo-controlled studies on the use of acarbose in diabetic patients indicated that acarbose treatment was associated with a 35% risk reduction of cardiovascular disease.[5]

Its a complex oligosaccharide which reversibly inhibits α- glucosidase present in the brush border of small intestinal mucosa. It slows down and decreases digestion and absorption of polysaccharides and sucrose and thus PPBS is reduced without increasing insulin levels. It's a mild anti hyperglycemic and not a hypoglycemic and may be used as an adjuvant to diet in obese diabetics. Its minimally absorbed but produces flatulence and loose stool due to fermentation of unabsorbed carbohydrates.[29]

The properties of Acarbose make this a promising agent for the treatment of patients presenting hyperglycemia, hyperinsulinemia and hypertension. Inhibition of α-intestinal glucosidases retards the absorption of ingested carbohydrates and attenuates PPBS and hyperinsulinemia. A potential beneficial effect of the drug on insulin resistance due to the improvement in hyperglycemia and glucotoxicity may also contribute to reducing blood pressure (BP) in hypertensive diabetic patients.[30]

Review of Literature

REVIEW OF LITERATURE

TMS Wolever et al reported that long-term use of Acarbose therapy in subjects with NIDDM on weight-maintaining diets, may result in a small weight loss, but has no effect on energy or nutrient intakes. The weight loss induced may be due to reduced doses of concomitant oral agents and insulin and partly due to energy loss due to increased colonic fermentation.[31]

Boniface J Lin et al in their studies on Asian Type 2 diabetic patients concluded the possible benefits of adjunctive Acarbose therapy in addition to the use of diet and Sulfonylureas. It was significantly superior to placebo as observed in the reduction of primary efficacy parameter HbA_{1C}. It reflects the long-term control of glycemic control and reduces risk of microvascular endpoints. A major problem using oral antidiabetic drugs such as Sulfonylureas is decreasing ability to control blood glucose levels satisfactorily. Acarbose acts as an antihyperglycemic agent and has the additional benefit of reducing weight gain.[8]

Gabriele Mertes concluded in his study that Acarbose was found to be generally well tolerated with a lower incidence of side effects than placebo-controlled studies. Patients showed marked improvements in a range of metabolic parameters over the 5-year course of the study. It demonstrated its usefulness both as first-line monotherapy and as an important addition to other antidiabetic drugs for improving metabolic controls in patients with Type 2 diabetes. The majority of the patients were sufficiently treated with a low dose and proved to be a safe drug in a high risk patient population.[32]

Chii-Min Hwu et al discussed that acarbose offers advantages as a combination therapy with insulin in the treatment of Type II diabetes and works well in Asian diabetic patients. Owing to its particular mode of action, it improves the therapeutic efficacy of concomitant insulin without the risk of weight gain and hypoglycemia.[33]

Chunlin Li et al stated that Acarbose can be used as a first-line therapy or in combination with other glucose-lowering agents for type 2 DM and it was found to be associated with improvement in glycemic parameters, and was safe and well tolerated. In addition, it will maintain glycemic control and a good tolerability profile over the long term in Type II diabetic patients.[1]

L. Sangiorgio et al suggested that addition of acarbose was found to be effective in improving glycemic control in overweight elderly Type II diabetic patients with poor glycemic control on OHA or insulin regimes. Acarbose is an inhibitor of α-glucosidase and acts directly at the gastrointestinal level slowing down the intestinal absorption of glucose and eventually reduce the rapid increase in glycemia induced by a meal rich in carbohydrates.[28]

B.Brooks et al stated that after Acarbose therapy was initiated, patient improves glycemic control and changes post-prandial energy expenditure of Type II diabetic patients in secondary failure. The magnitude of long term reduction in hyperglycemia differs amongst individuals. This is largely due to intrinsic variations in patients' response to Acarbose rather than differences in medication compliance or dietary composition.[34]

Jean-Louis Chiasson et al revealed that Acarbose improved long-term glycemic control in patients with non-insulin-dependent diabetes mellitus regardless of concomitant antidiabetic medications. Our study shows that it is a safe drug for treating patients with non-insulin-dependent diabetes mellitus. Over 1-year study period, acarbose did not affect hematologic, biochemical, or liver function test results. Our study also strongly suggests that the drug does not induce nutritional malabsorption because the serum concentrations of vitamins and minerals remained unchanged in patients treated with acarbose[16]

M. Hanefeld et al examined that Intervention with acarbose can prevent myocardial infarction and cardiovascular disease in Type II diabetic patients while most of them are already on intensive concomitant cardiovascular medication. acarbose treatment of type 2 diabetes has shown preventive effects on myocardial infarction and any cardiovascular events. This may be explained by a reduction of postprandial hyperglycaemia and improvement in other features of the metabolic syndrome.[35]

Peter N Bavenholma et al reported that reduced ability to control blood glucose level results in postprandial hyperglycaemia, which affects the vascular endothelium and leads to the development of CVD. This impact may be attenuated by the use of Acarbose. The results from the STOP-NIDDM trial and the meta-analysis suggest that it can reduce the risk of CVD and support a scientific rationale for the early use of Acarbose to reduce the progression from IGT to established type 2 diabetes and to reduce the risk of CVD.[36]

Floris A Van de Laaar et al examined in their systematic review of 41 randomized studies on the efficacy of AGIs, statistically significant effects on GHb and fasting blood glucose, post load glucose and insulin levels, and BMI has been found. There was no increase in effect on GHb for acarbose dosages higher than 50 mg tid. In general, most evidence and the best results were found for acarbose. AGIs have clear beneficial effects on glycemic control and postload insulin levels but not on plasma lipids.[7]

Robert Coniff et al stated that Acarbose represents a new approach to the management of NIDDM, modulating gastrointestinal carbohydrate metabolism to control postprandial hyperglycemia and to maximize long-term glycemic control. It usually in doses of up to 100 mg three times daily for periods up to 16 weeks, was significantly superior to placebo with respect to the mean reduction in HbA1C levels and mean l-hour postprandial glucose levels.[6]

J M Ghosh examined that Acarbose when combined with modified diet resulted in significant decline in postprandial blood glucose in Type II DM cases, large majority of which were cases of secondary failure with oral hypoglycemic agents (OHA). It is suggested that before adding Insulin in cases of OHA failure, adequate trial of low G.I. diet and Acarbose should be routinely tried.[37]

Michio Shimabukuro et al suggested that Acarbose might reduce macrovascular complication by avoiding endothelial injury in postprandial hyperglycemic status. It might be a promising post prandial therapy in treating endothelial function seen in patients with type 2 diabetes mellitus by decreasing the postprandial glucose excursion. It was found that even a single loading of test meal was shown to impair

endothelial function in type 2 diabetic patients, and the postprandial endothelial dysfunction was improved by a prior use of Acarbose.[5]

Uwe Zeymer examined that Acarbose is the first anti-diabetes agent that has been shown in a randomised, placebo-controlled trial to delay the progression of glucose intolerance to diabetes and reduce the risk of cardiovascular events. These attributes provide a strong rationale for the use of such agents to reduce cardiovascular risk in patients with impaired glucose control. The results of the STOP-NIDDM and the acarbose meta-analysis provide strong evidence that preventing postprandial hyperglycaemia reduces the risk of cardiovascular events in patients with impaired glucose tolerance and overt Type II diabetes.[21]

P. Rosenbaum et al reported Acarbose shows benefits in terms of the glycemic control of hypertensive diabetic patients previously treated with diet alone or combined with sulfonylurea. The administration of acarbose to sulfonylurea-treated patients may prevent weight gain. Such effects are desirable taking into account the elevated cardiovascular risk of these patients. Acarbose monotherapy or combined with sulfonylurea was effective in improving glycemic control in hypertensive diabetic patients. Acarbose induced improvement in metabolic control may reduce BP in these patients. [30]

Markolf Hanefeld suggested that Acarbose is a drug with a novel mechanism of action, which attenuates postprandial hyperglycemia by delaying carbohydrate absorption. This is achieved by competitive inhibition of key intestinal enzymes. It has been shown to be an effective oral antidiabetic agent that improves glycemic control, producing HbA_{1C} reductions of 0.6 to 2.5 percentage points. Good glycemic

control is of major importance in trying to prevent secondary diabetic complications and the increased mortality in patients with NIDDM.[26]

Henrik Wagner et al stated that in subjects with mild type 2 diabetes, exercise training improved insulin sensitivity but had no effect on glycemic control. The addition of acarbose to exercise, however, was associated with significant improvement of glycemic control and possibly cardiovascular risk factors. When exercise training was combined with acarbose treatment a decrease in HbA_{1C} level and fasting plasma glucose concentration was observed. Treatment with Acarbose alone was associated with improvement in blood pressure and β-cell function, as reflected by a significant decrease in plasma proinsulin level.[38]

Patrick Phillips et al suggested that Acarbose therapy have a beneficial effect in reducing the overall glycemic control in overweight patients insufficiently controlled by Metformin alone. HbA1c levels showed a clinically significant difference of 1.02% in acarbose patients after 24 weeks of treatment compared to placebo patients . The addition of acarbose to metformin monotherapy provides an efficacious and safe alternative for glycemic improvement in overweight type 2 patients inadequately controlled by metformin alone.[25]

Su Jian-bin et al stated that in patients with higher mean amplitude of glycemic excursions (MAGE), treatment with acarbose obviously decreases hypoglycemia, postprandial glycemia and total insulin used per day. It's an α-glucosidase inhibitor

and competitively inhibit the α-glucosidase and prevent it from hydrolyzing disaccharides to monosaccharides and leads to decrease peak blood glucose concentration after meal. Therefore total insulin used per day consequently reduced with the decline of postprandial glycemia, and hypoglycemia. Combination therapy of premixed insulin twice daily with acarbose may be an effective and convenient treatment for patients.[39]

Chien- Wen Chou et al examined that both obese and non-obese type 2 diabetic patients showed decreased HbA1c after acarbose therapy. Obese patients had an additional benefit of a decrease in their previously elevated ALT and triglyceride levels. It usually have some beneficial effects on the elevated serum ALT levels in obese diabetic patients. In those with impaired glucose tolerance, it has been demonstrated to improve insulin secretion and insulin sensitivity.[12]

Tomomi Fujisawa et al suggested that 50 mg Acarbose and 0.3 mg Voglibose had similar overall effects on postprandial hyperglycemia as well as subjective symptoms, but marked inter individual variation will exist. Subjective symptoms may be a predictor of the divergent clinical response to each agent. It is also possible that postprandial hyper glycemia is affected by differences in the glycemic index of carbohydrates in the diet. The present results suggest the usefulness of subjective symptoms as a predictive marker for clinical efficacy of each agent, which is applicable for better management of diabetes mellitus.[40]

Chang-Yu Pan et al examined that Acarbose was efficacious and safe in the reduction of hyperglycaemia and hyperinsulinaemia in IGT subjects, indicating a potential benefit for the delay or prevention of onset of Type 2 diabetes. A low dosage

of acarbose in the present study proved to be sufficient for the improvement of metabolic control and was well tolerated. It also adds evidence that pharmacological intervention with acarbose can be effective in Chinese IGT subjects. [41]

H. Delgado et al reported that treatment with Acarbose is efficient even in diabetic patients presenting a good glucose control without any other associated treatment. By decreasing the elevated post prandial blood glucose, it improves both insulin sensitivity and insulin secretion. It usually allow a significant improvement in post prandial glycemic peaks in well controlled Type II diabetes patients. It disclose Acarbose efficacy as monotherapy in well controlled obese Type II diabetic patients.[42]

Shi-Dou Lin et al suggested that Acarbose - Metformin combination therapy is more effective in reducing intraday and interday glucose variability without increasing the duration of hypoglycemia compared with the Glibenclamide – Metformin combination. Asian people typically consume a higher proportion of carbohydrates in their diet, and this reflects the more important role of postprandial hyperglycemia. Acarbose, as a result, may be an appropriate add-on drug for Type II diabetic patients inadequately controlled with Metformin alone.[43]

Lam K S et al examined that the use of Acarbose in moderate doses in NIDDM patients inadequately controlled on conventional oral agents resulted in beneficial effects on glycemic control, especially postprandial glycemia, and mean body weight. Additional use of acarbose can be considered as a useful alternative in such patients if they are reluctant to accept insulin therapy.[44]

O. Schnell et al investigated the effect of Acarbose in patients with type 2 diabetes with newly initiated insulin treatment who had previously been insufficiently controlled with oral antihyperglycaemic agents. As adjunct administration to newly initiated insulin therapy, acarbose enhances the optimization of blood glucose control in patients with type 2 diabetes. [45]

N. Scorpiglione et al evaluated in their study an integrated evaluation of the overall effectiveness of acarbose in clinical practice. The benefits of the drug in an unselected population of non-insulin-dependent diabetes mellitus patients are significant but of marginal clinical relevance. Patients on long term treatment, particularly through possible postponement of secondary oral antidiabetic agent failure, will allow a reliable definition of the cost-effectiveness of this complementary component of anti-diabetic strategy. [46]

Chan J C et al examined in an Asian multicenter clinical trial involving six ethnic groups, Acarbose 100 mg tid. was an effective, safe, and generally well-tolerated therapy in Type II diabetic patients with dietary failure. In some patients with troublesome gastrointestinal symptoms, a lower dosage may be necessary. Here the efficacy and tolerability of acarbose compared with placebo in Type II diabetic patients previously treated with diet .[47]

Rury R. Holman et al reported that Acarbose significantly improved glycemic control over 3 years in patients with established Type II diabetes. Careful titration of acarbose dose is needed in view of the increased noncompliance rate seen secondary to the known side effects. It is particularly useful as an alternative first-line treatment

for type 2 diabetes, when diet alone is insufficient and targets postprandial hyperglycemia. This specific mode of action also means that acarbose can be combined successfully with other agents which primarily reduce fasting hyperglycemia. The lack of any deleterious effects with respect to clinical outcomes and the absence of effect on body weight are desirable features.[48]

Plan Of The Study

PLAN OF THE STUDY

PHASES	STEPS	ACTIVITY	TIME PERIOD
PHASE 1	STEP 1	Identification of target areas for possible study	June 2011
	STEP 11	Literature survey	June 2011
	STEP 111	Defining crieteria and standards	July 2011
	STEP 1V	Designing of data collection form	July 2011
PHASE 11	STEP V	Collection of data through patients case sheet and treatment chart	July 2011-January 2012
PHASE 111	STEP V1	Analysis of data	January 2012

Overview

OVERVIEW

Diabetes mellitus is a heterogeneous group of disorders which occur secondary to various genetic predispositions and precipitating factors. It is characterized by disorders in carbohydrate, fat and protein metabolism and it occurs due to an absolute or relative deficiency of insulin and abnormally high amounts of glucagon and other counter regulatory hormones. In particular, rates of type 2 diabetes are rising in developing countries and are undergoing an epidemiological transition from communicable to chronic diseases.[3] It usually affects more than 120 million people world-wide, and it is estimated that it will affect about 220 million by the year 2020. It is usually irreversible though patients can lead a reasonably normal lifestyle.[49]

It is a chronic disease and begins with an early asymptomatic phase characterised by insulin resistance, and progresses to postprandial hyperglycaemia and, eventually to overt type 2 diabetes. The principal metabolic defects in type 2 diabetes are insulin resistance, beta-cell dysfunction, and increased hepatic glucose production. The DCCT demonstrated that level of glycemic control will correlate the appearance and progression of retinopathy, nephropathy and neuropathy.[10]

The two major classifications of DM are Type I and Type II. These were formerly known as Insulin Dependent and non Insulin Dependent Diabetes Mellitus. They differ in clinical presentation, onset, etiology and progression. Both are associated with microvascular and macrovascular complications. Diagnosis of diabetes is usually made by three crieteria:-

- Fasting plasma glucose of $\geq$ 126mg/dl
- A 2 hr value from a 75g oral glucose tolerance test of $\geq$ 200 mg/dl

❖ A casual plasma glucose level of ≥ 200 mg/dl with symptoms of diabetes [50]

Type 1 has been considered as a disease of sudden onset but the development occurs as a slow process of progressive immunological damage. Obesity is considered as an important risk factor for it. Its associated with hyperinsulinaemia and marked insulin sensitvity.[6] Diet therapy usually remains as the cornerstone of the treatment strategies for non-insulin-dependent diabetes mellitus. It aims to maintain ideal body weight and to reverse any metabolic abnormalities associated with the disease.

PPBS and elevations in HbA_{1C} levels have been considered as the long term complications of diabetes. Not all patients respond adequately to diet, exercise, or treatment with oral drugs, alternate therapies have been investigated. Acarbose which is the first α-glucosidase inhibitor exerts its activity by reversibly inhibiting the enzymatic cleavage of complex carbohydrates to simple sugars which results in a reduction in PPBS and subsequently, reductions in HbA1c levels.[51]

Type 1 treatment necessitates insulin therapy while the treatment of type 2 DM often necessiates use of multiple therapeutic agents including oral antihyperglycemics and insulin to obtain glycemic goals. Prevention strategies for type 2 DM are established which include lifestyle changes, dietary restriction of fat, aerobic exercise and weight loss.[5] PPBS has been shown to be an independent cardiovascular risk factor. The properties of Acarbose makes it a promising agent for the treatment of patients presenting hyperglycemia, hyperinsulinemia and hypertension and attenuates PPBS.[10]

Etiologic Classification Of Diabetes Mellitus

1) Type 1 Diabetes (β cell destruction leading to absolute insulin deficiency)
   a) Immune mediated
   b) Idiopathic
2) Type 2 Diabetes (secretory defect with insulin resistance)
3) Other specific types
   a) Genetic defects of β cell function
   b) Genetic defects in insulin action
   c) Disease of the exocrine pancreas:-PancreatitiS, Neoplasia, Cystic fibrosis
   d) Endocrinopathies :- Acromegaly, Cushing's syndrome
   e) Drug or chemical Induced:- Nicotinic acid, Glucocortecoids, Thiazides
   f) Infections:-Congenital rubella, Cytomegalovirus
   g) Uncommon forms of immune mediated Diabetes:-Stiff-man syndrome, Anti Insulin Receptor Antibodies
4) Gestational Diabetes mellitus[3]

Etiology

Diabetes mellitus has been associated with many etiological factors which includes obesity, increasing age, heredity, emotional stress, autoimmune β cell damage, endocrine diseases (cushings disease),vasculitis in tissues highly perfused with capillaries (eye, kidney), insulin receptor or post insulin receptor defects, drugs (cortecosteroids, thyroid drugs, thiazide diuretics).[52] Type 1 has been widely believed to be a disease of clinically rapid onset but the development is related to a slow process of progressive immunological damage. Other factors that precipitate clinical diabetes may be caused by infection when β cells in the pancreas falls below 5-10%.

One of the main cause of type 1 DM is autoantibodies directed against pancreatic islet which appears in circulation and predate the clinical onset. If one child in a family has type 1 diabetes, each sibling has a 6% risk of developing diabetes by age. [31] If siblings are HLA-identical, the risk rises to about 20%. Longer-term follow-up has shown that the lifetime risk of diabetes in first-degree relatives is considerably greater than this.[10] Type 2 diabetes has a strong genetic predisposition. If a parent has type 2, the risk of a child eventually developing type 2 is 5- 10 % compared with 1-2% for type. Mainly central obesity where subcutaneous fat is deposited intra abdominally is considered as the most risk factor.[6]

Epidedmiology

Diabetes mellitus is present in roughly 16 million citizens. Around 675000 people have type 1 and majority of those remaining have type 2 diabetes. Girls experience a peak incidence of type 1 between 10 and 12 years where as boys have higher incidence between 12 and 14 years. Diabetes in people older than 20 accounts for 90-95 % of all cases.[1] In the UK Prospective Diabetes Study (UKPDS) it has been shown that intensive glucose control significantly reduced the risk of microvascular complications by 25%.[12] Type 1 DM accounts for upto 10% of all cases of DM and results from an autoimmune destruction of the pancreatic β cell. Type 2 DM accounts for about 90% of all cases of DM.[53]

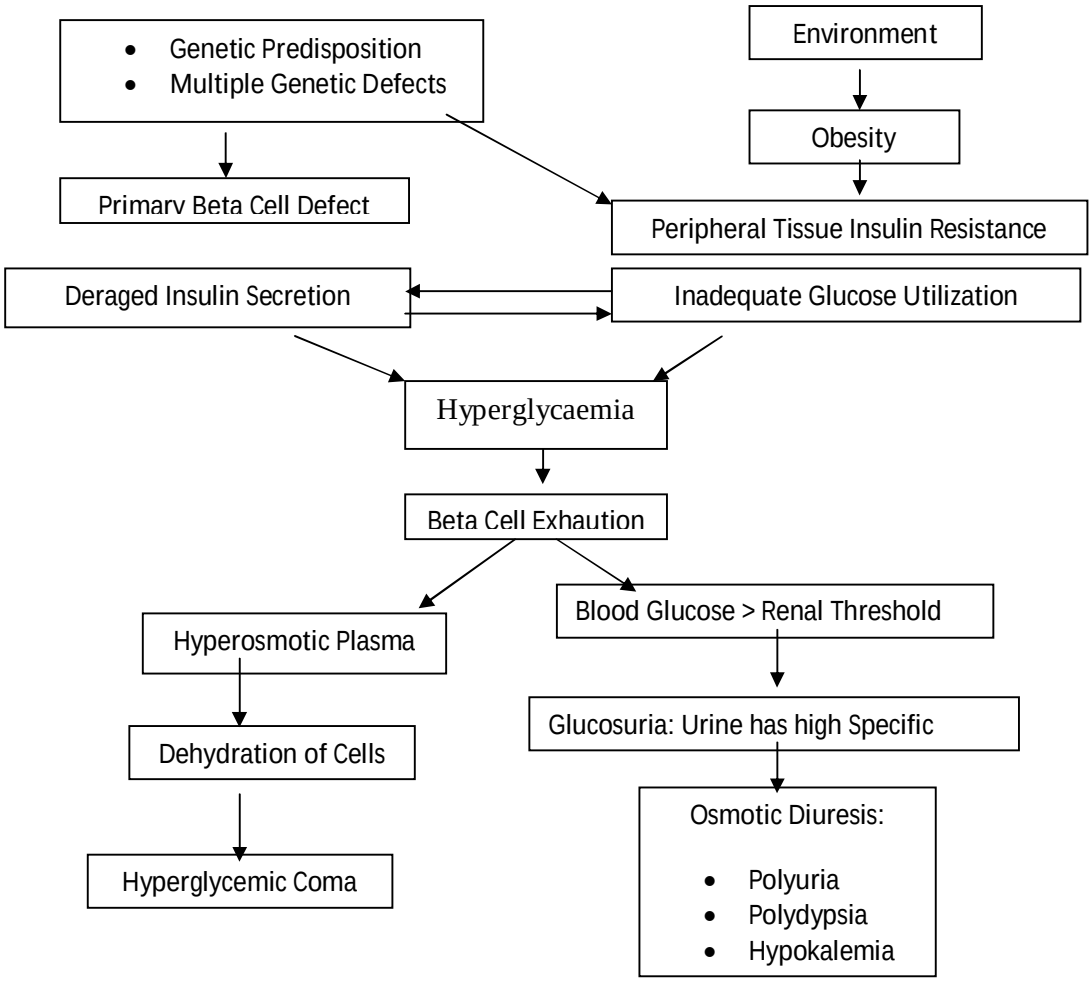
Pathogenesis

Type II DM

Impaired insulin secretion and resistance to the action of insulin characterize patients with type 2 diabetes. In the presence of insulin resistance, glucose utilization by tissues is impaired, hepatic glucose production is increased, and excess glucose

accumulates in the circulation. Type 2 diabetes is associated with a variety of disorders, including obesity, atherosclerosis, hyperlipidemia, and hypertension.[54]

Pathogenesis of Type II Diabetes Mellitus



Signs and symptoms

Type 1 diabetes usually presents typically with polydipsia, polyuria, polyphagia, weakness, weight loss, dry skin and ketoacidosis. Type 2 Diabetes typically is slow in onset and is often unaccompanied by symptoms. The different features include glucosusuria, proteinuria, micro aneurysms and retinal exudates. Other symptoms of

hyperglycemia include blurred vision, tingling or numbness of the extremities, skin infections, itching , drowsiness and irritability[55]

Microvascular complications

These effects of hyperglycemia range from minor symptoms to life threatening metabolic complications. The two serious short term complications are:- diabetic ketoacidosis (DKA) and non ketotic hyperosmolar syndrome (NHKS). DKA is life threatening condition that usually occur secondary to an insulin deficit. It may occur in patients who have an active infection, those who have discontinued insulin therapy or those subjected to other forms of stress.[21]

Retinopathy - After 20 years from the onset of diabetes over 90% of people with type1 and over 60% of people with type II will have retinopathy.[4] Early onset of retinopathy may be reversed with improved glycemic control. Laser photocoagulation has improved slight preservation in diabetic retinopathy.[56]

Nephropathy - In diabetic renal disease the kidneys become enlarged and the glomerular filtration rate initially increases. The presence of nephropathy is indicated by the detection of microalbuminuria. If higher amounts of albumin are detected, its termed as proteinuria or macroalbuminuria.

Peripheral Neuropathy - It's the progressive loss of peripheral nerve fibres resulting in nerve dysfunction. It may lead to distal sensory symptoms which is evident in the feet. The manifestations of autonomic neuropathy are diabetic impotence, bladder dysfunction, gastroparesis and dry skin.[57]

Macrovascular disease

The different macrovascular complications include cardiovascular disease (coronary heart disease and stroke) and peripheral vascular disease

Cardiovascular disease:- Its one of the most common cause of death in patients with type 2 DM.. The different cardiovascular disease risk factors are smoking and dyslipidaemia. Silent MI is more common in diabetic patients and may be due to cardiac autonomic neuropathy

Peripheral Vascular Disease:- It affects blood vessels outside heart. It often affects arteries of the legs and may give rise to intermittent claudication which is usually experienced on walking. The iliac vessels can also be affected and causes buttock pain and erectile dysfunction.

Treatment

Oral Hypoglycemic Drugs

These drugs lower blood glucose levels and are effective orally

- Sulfonyl Ureas - Tolbutamide, Chlorpropamide, Glibenclamide, Glipizide, Glimipride
- Biguanides - Phenformin, Metformin
- Meglitinide Analogues - Repaglinide, Nateglinide
- Thiazolidinediones - Rosiglitazone, Pioglitazone
- Alpha Glucosidase Inhibitors - Acarbose, Miglitol, Voglibose

These drugs are indicated only in type II diabetes, when not controlled by diet and exercise.[29]

InsulinTherapy

Insulin is the mainstay for treatment of virtually all Type I DM and many Type II DM patients. When necessary, insulin may be administered intravenously or intramuscularly; however, long-term treatment relies predominantly on subcutaneous injection of the hormone.[22] Insulin therapy may induce an increase in weight, worsen insulin resistance and have the possibility to contribute to macroangiopathic complications.

Properties of currently available Insulin preparation [57]

TYPE	APPEARANCE	ZINC CONTENT, mg/100 units	BUFFER	ONSET	PEAK	DURATION
Rapid						
Regularsoluble (crystalline)	Clear	0.01-0.04	None	0.5-0.7	1.5-4	5-8
Lispro	Clear	0.02	Phosphate	0.25	0.5-1.5	2-5
Aspart	Clear	0.0196	Phosphate	0.25	0.6-0.8	3-5
Glulisine	Clear	None	None	—	0.5-1.5	1-2.5
Intermediate						
NPH (isophane)	Cloudy	0.016-0.04	Phosphate	1-2	6-12	18-24
Lente	Cloudy	0.2-0.25	Acetate	1-2	6-12	18-24
Slow						
Ultralente	Cloudy	0.2-0.25	Acetate	4-6	16-18	20-36
Protamine zinc	Cloudy	0.2-0.25	Phosphate	4-6	14-20	24-36

Methodology

METHODOLOGY

Objective:

To study the long term efficacy of Acarbose in improving glycemic control in patients with Type II diabetes mellitus

Study Design:

It is a prospective observational study.

Study Site:

The study was conducted in the department of Diabetology, Kovai Medical Center and Hospital, a multispecialty hospital in Coimbatore, Tamilnadu.

Study Period:

The study was conducted from June to January 2012.

Study Population:

Both male and female patients diagnosed as Type II Diabetes Mellitus.

Patients having glycosylated hemoglobin (HbA_{1C}) above the upper limit (more than 6.5%)

Sources of Data:

The data was collected from various sources such as patient's case sheet, treatment chart, laboratory reports and also through direct patient interview.

Study Procedure:

In this prospective study both male and female patients diagnosed with Type II Diabetes mellitus having HbA_{1C} value more than 6.5% were included and those

having type 1 DM taking insulin as sole therapy and patients with chronic intestinal disease are excluded. All the patients who fulfill the inclusion crieteria are taken for the study. The laboratory values and medications are noted from the patient's chart.

Values such as FBS, PPBS, HbA_{1C}, BMI are noted at the initial visit and the therapeutic efficacy of the drug in reducing these parameters were determined during the next review. Acarbose was usually given in addition to the current diabetes medications. Another group was also included in the study where patients taking other oral hypoglycemic agents except Acarbose. The percentage reduction in blood glucose profile in both groups were calculated and the therapeutic efficacy of the drug was determined

Data are collected from the data entry form which gives values of blood glucose profile. Baseline and review values were compared by paired students 't' test. The significant reduction produced in blood glucose value was determined.

Also the percentage reduction in blood glucose profile produced by Acarbose in obese and non obese patients was also calculated.

Data Analysis:

Data will be analyzed by using Graph Pad Prism 5.04 software. Results were expressed as percentage, mean and standard deviation. The result of the study was analysed by paired 't' test. All the test were two tailed Values of $P<0.05$ and $P<0.01$ were considered statistically significant.

Tables & Graphs

Table: 1 Shows gender wise distribution among study population (n=74)

S.No	Gender	Percentage of Patients
1	Male	56.7
2	Female	43.2

Fig-1 Gender wise Distribution

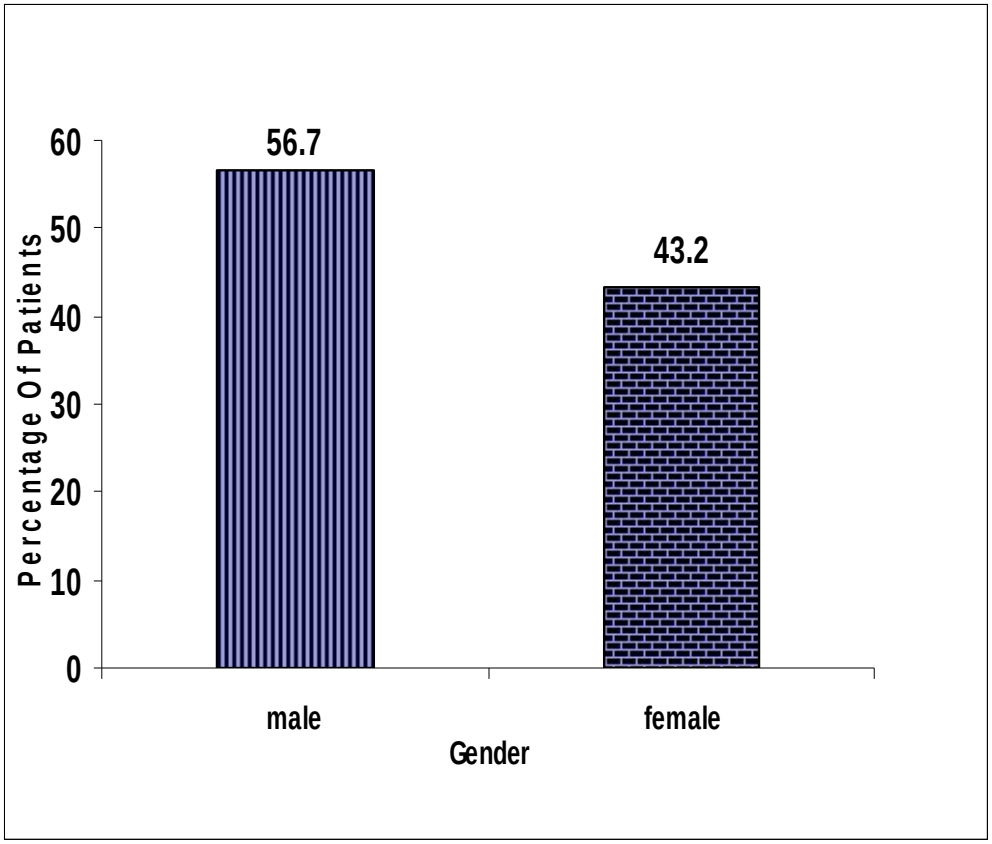


Table: 2 Shows mean age and gender wise distribution among study population

S.No	Gender	Age (mean±SD)
1	Male	55.14±11.28
2	Female	54.3 ± 10.6

Fig-2 Mean age and Gender wise Distribution

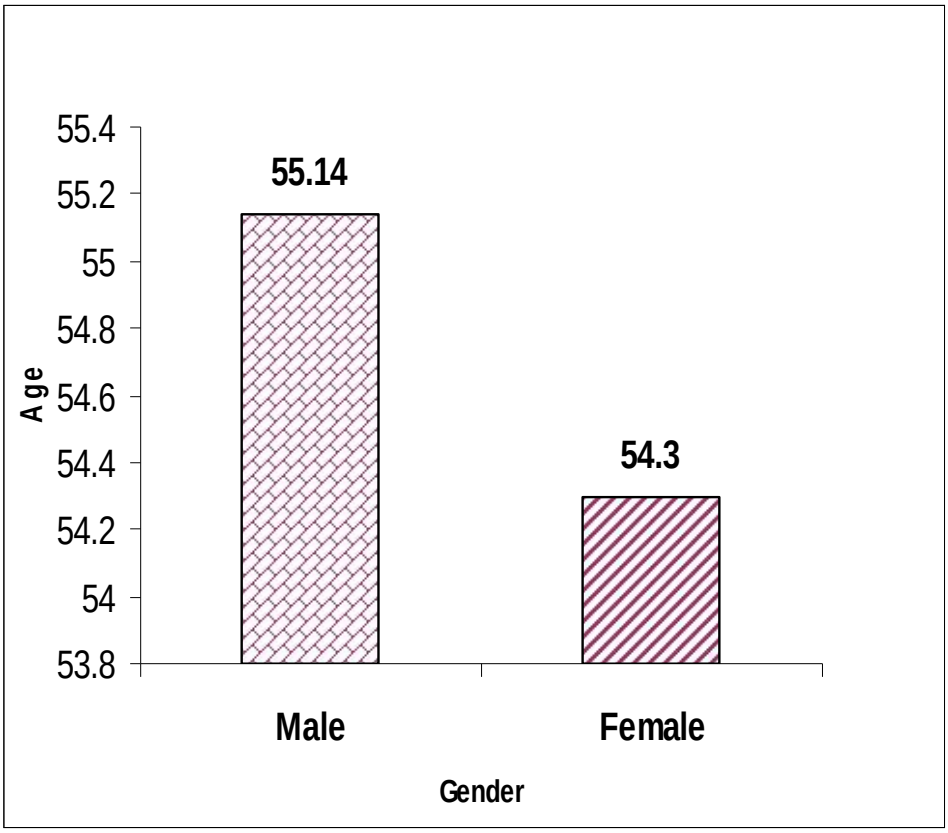


Table: 3 Shows categorization of body mass index among study population

BMI	Percentage of patients
Obese(≥25)	72.9
Non obese (<25)	27.02

Fig-3 Categorisation of BMI among study population

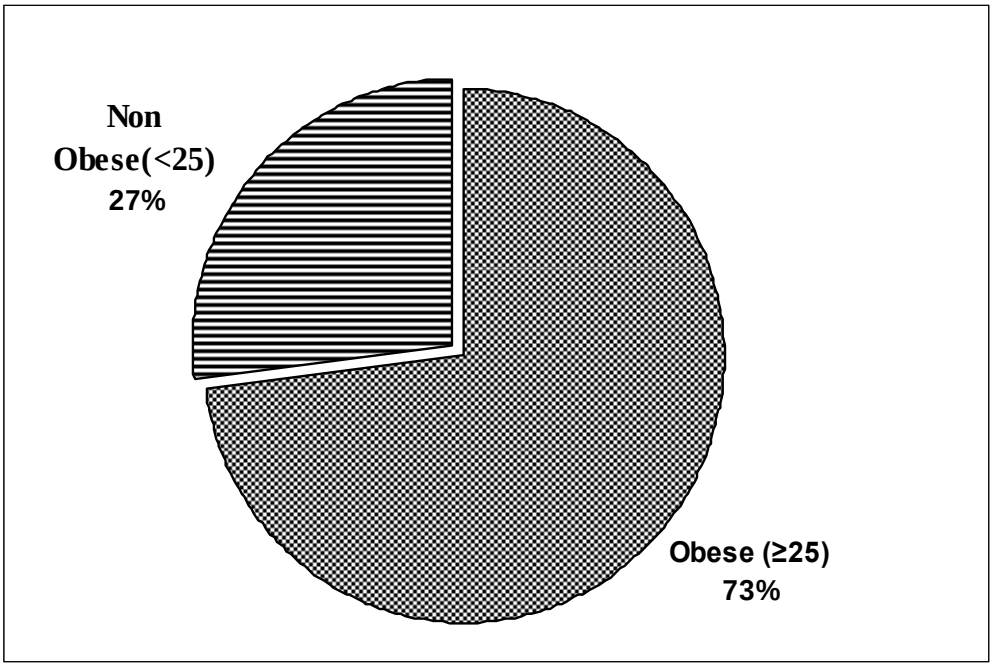


Table: 4 Shows family history of Type II Diabetes among study population

Family History	Percentage of patients
Yes	64.8
No	35.1

Fig- 4 Family History of Type II Diabetes among study population

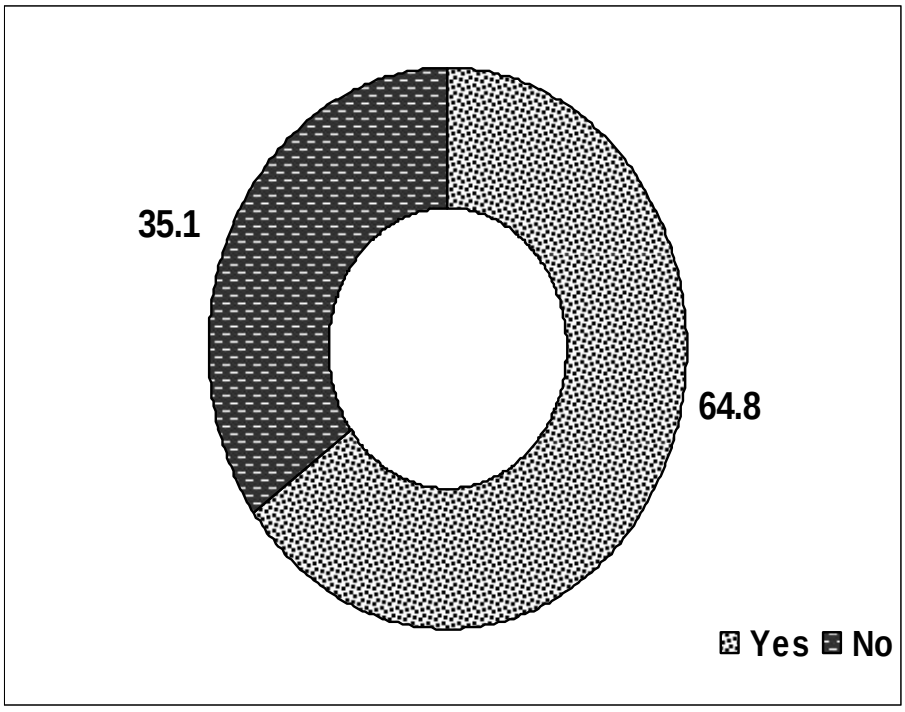


Table: 5 Shows duration of diabetes among study population

S.No	Duration of Diabetes	Percentage
1	0-5	22.9
2	6- 10	39.1
3	11-15	21.6
4	16-20	10.8
5	21-25	5.4

Fig-5 Duration of Diabetes Among study population

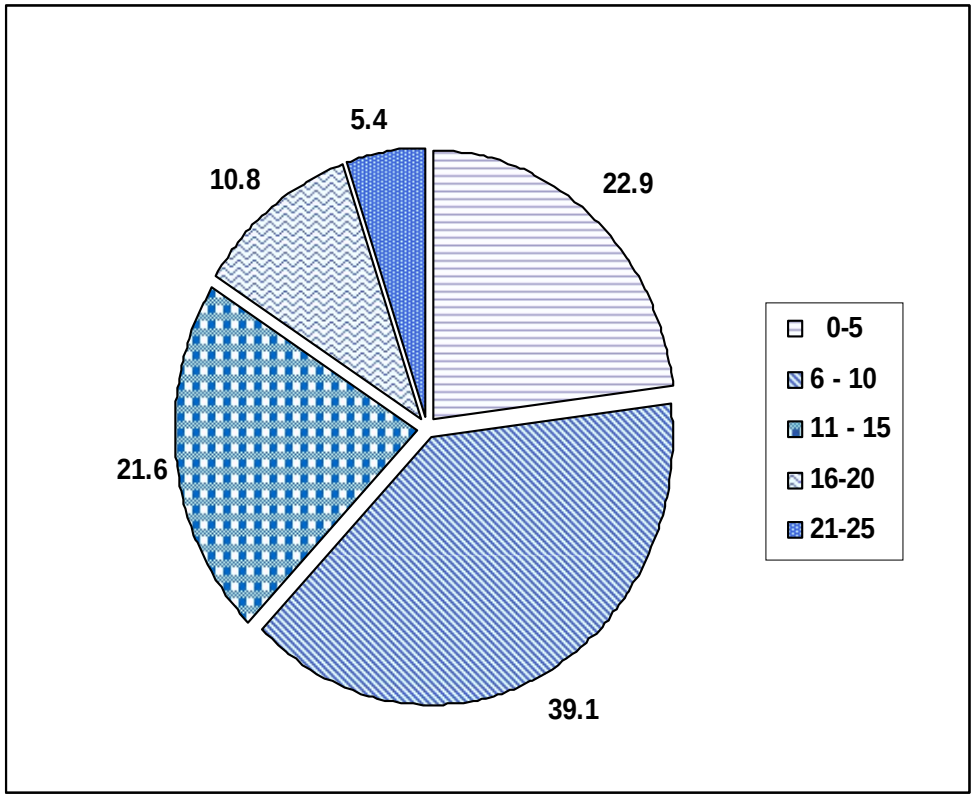


Table: 6 shows Past medical history among study population

S. no:	Past medical history	Percentage
1	Hypertension	60
2	Ischemic Heart Disease	20
3	Hypercholestrolemia	16.2
4	Reactive depression	9.4
5	Obesity	32.4
6	Hypothyroidism	18.9
7	Renal Impairment	29.7
8	Foot ulcer	43.2

Fig-6 Past Medical History among Study Population

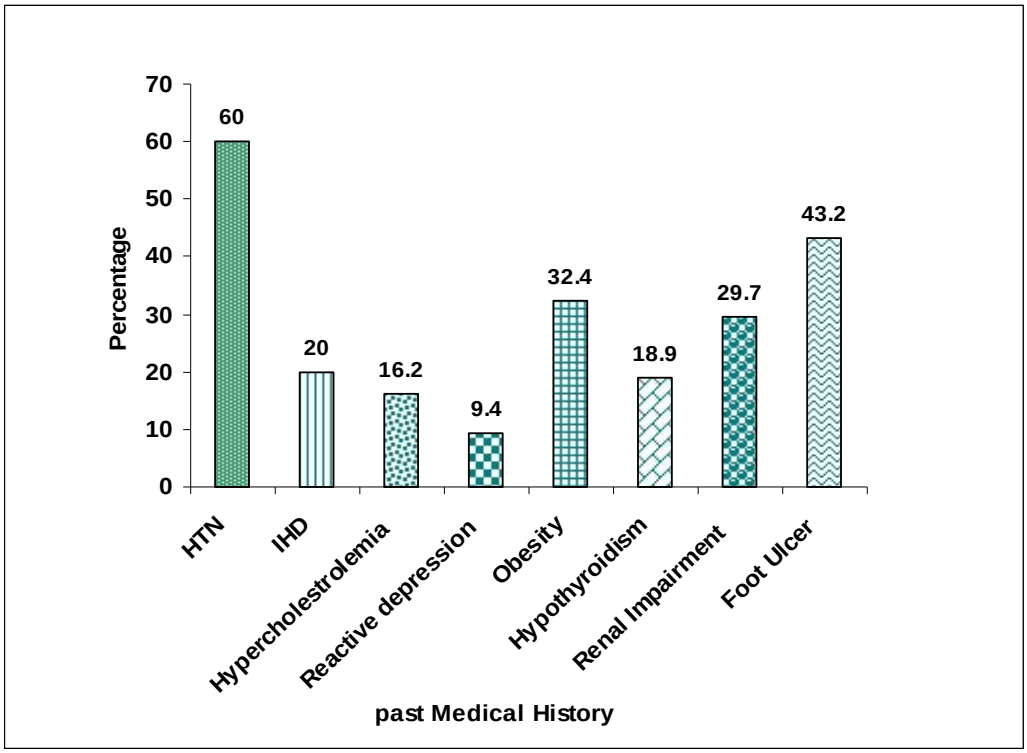


Table: 7 Shows Social Habits among Study Poulation

Smoking	Percentage Of Patients
Yes	67.5
No	32.4
Alcohol	Percentage Of Patients
Yes	59.4
No	40.5

Fig-7 Social habits Among study population

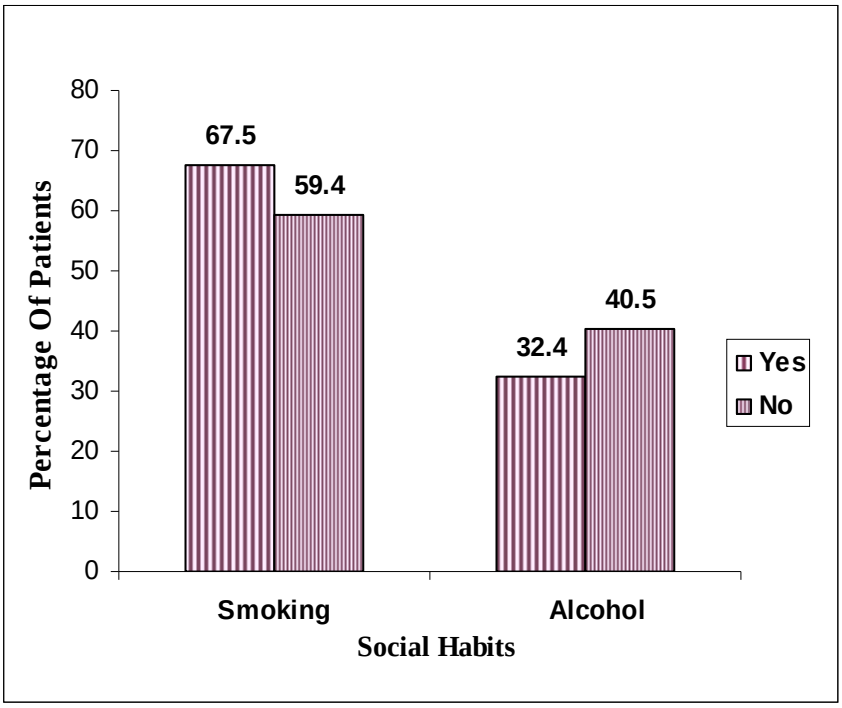


Table: 8 Diet Habits Among Study Population

S.No	Diet	Percentage of Patients
1	Diabetic	75.6
2	Non Diabetic	24.32

Fig-8 Diet Habits Among Study Population

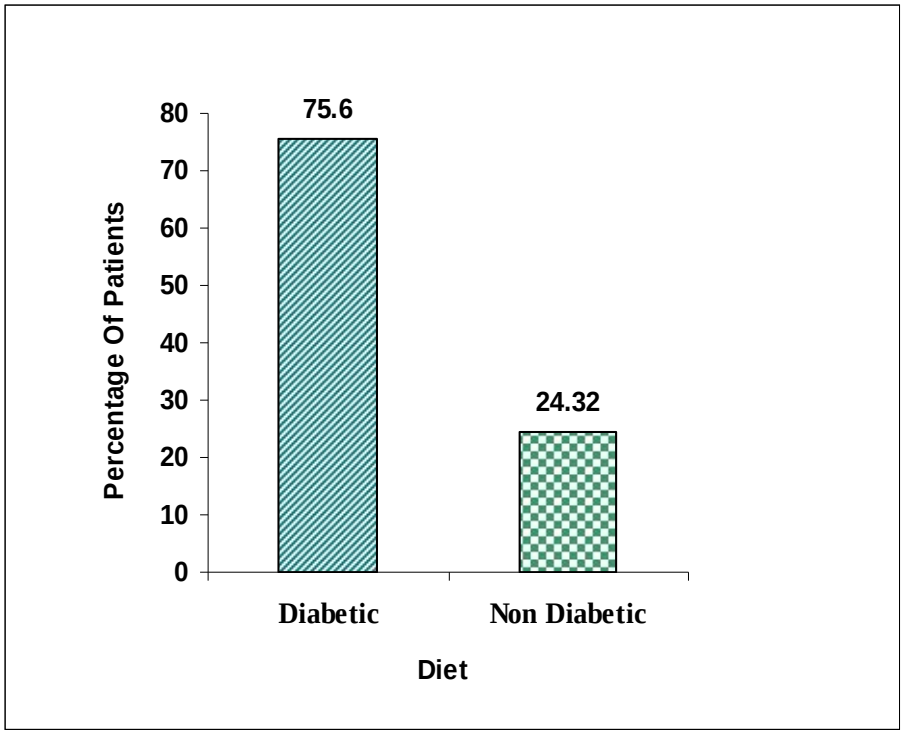


Table : 9 Dose wise Distribution Of Acarbose Among Study Population

Sl NO:	Prescribed Dose (Acarbose)	Percentage Of Patients
1	25mg	48.64
2	50 mg	37.83
3	100 mg	13.51

Fig-9 Dose wise Distribution Among Study Population

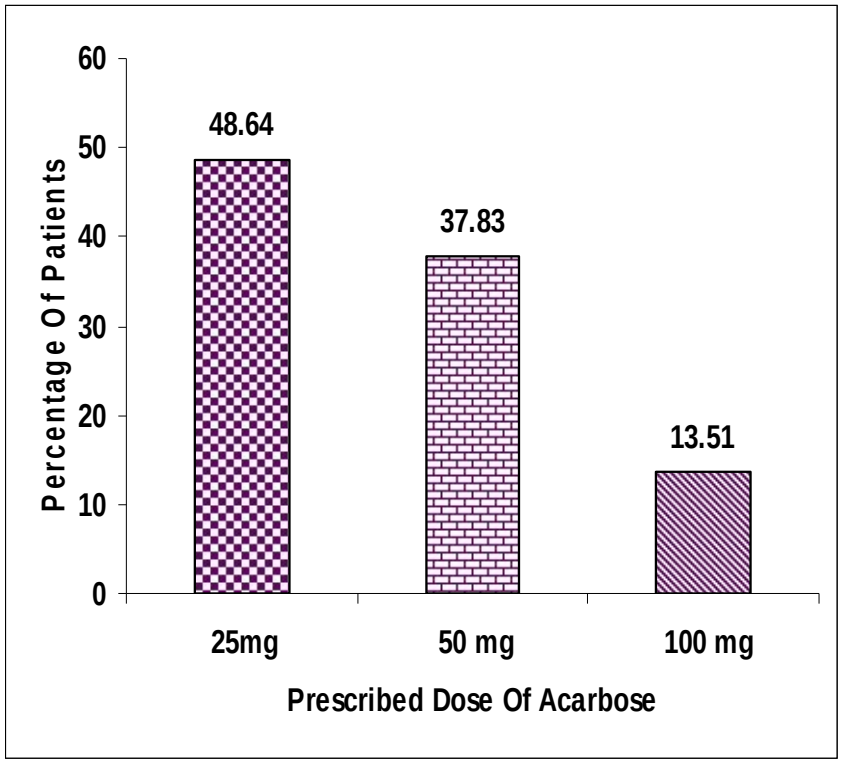


Table : 10 Percentage Reduction In Blood Glucose Profile In Obese And Non Obese Patients

S.No	Category	Percentage Reduced	Percentage Not Reduced
1	Obese	81.4	18.5
2	Non Obese	75	25

Fig-10 Percentage Reduction in blood glucose profile

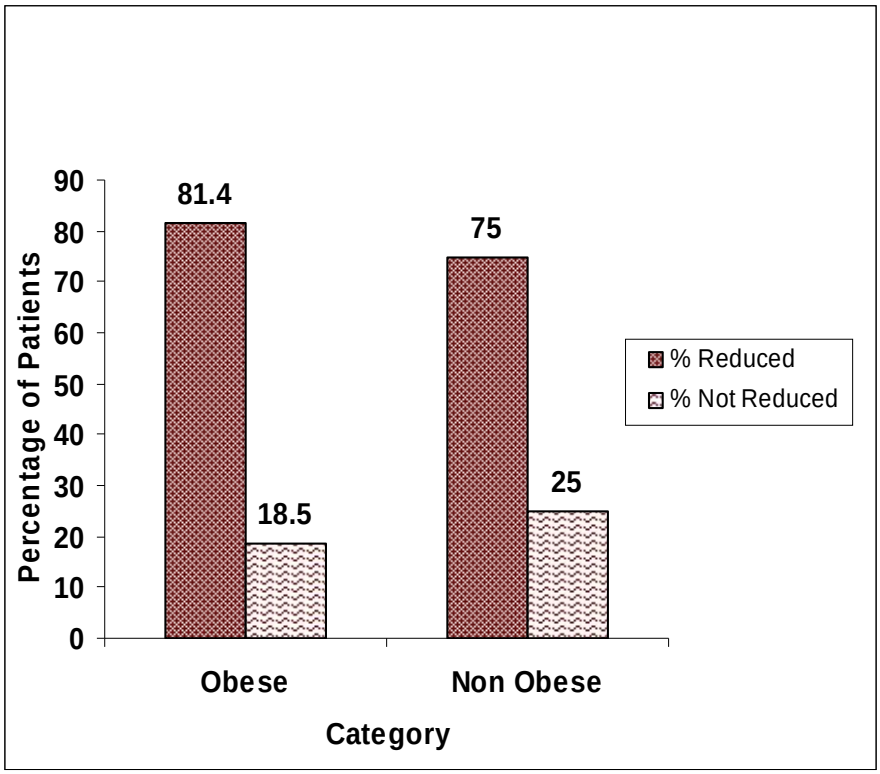


Table:11 shows Combination Of Acarbose With Other Antidiabetic Drugs

S. No	Drugs	Percentage
1	Acarbose + OralHypoglycemics	45.7
2	Acarbose + Insulin	34.2
3	Acarbose + Oral Hypoglycemics + Insulin	20

Fig-11 Acarbose in combination with other antidiabetic drugs

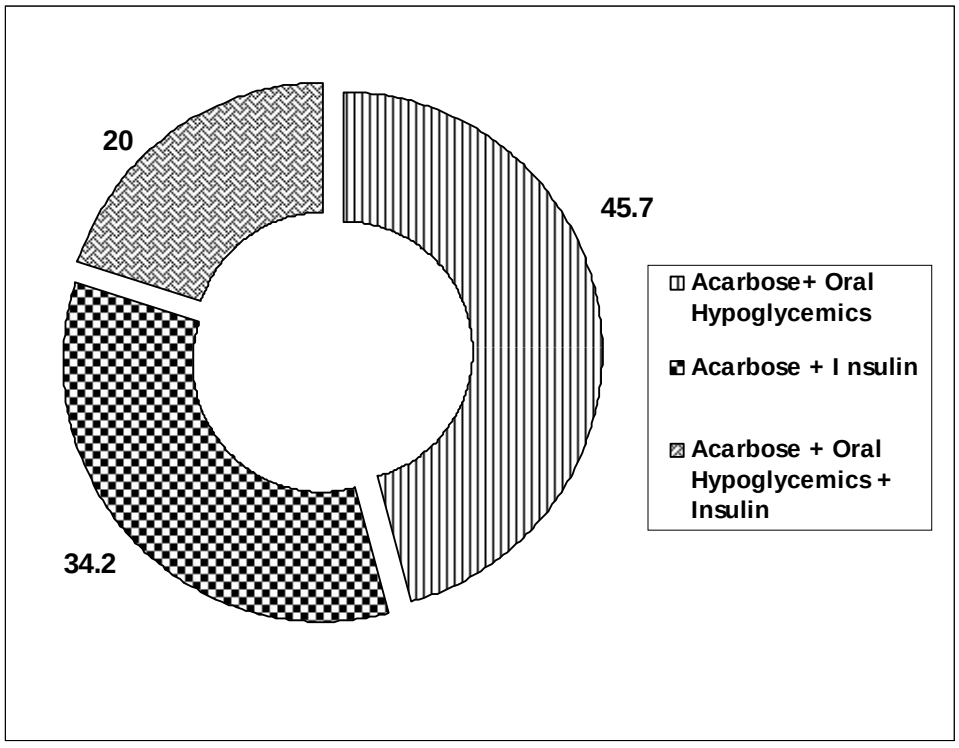


Table: 12 Shows Percentage Reduction in FBS in Acarbose Treated Group and Group Without Acarbose

S. No	Drugs	Percentage Reduction
1	Oral Hypoglycemics	9.37
2	Acarbose +Oral hypoglycemics	17.65
3	Acarbose + Oral Hypoglycemics + Insulin	18.80

Fig-12 Percentage reduction of FBS In each Study Group

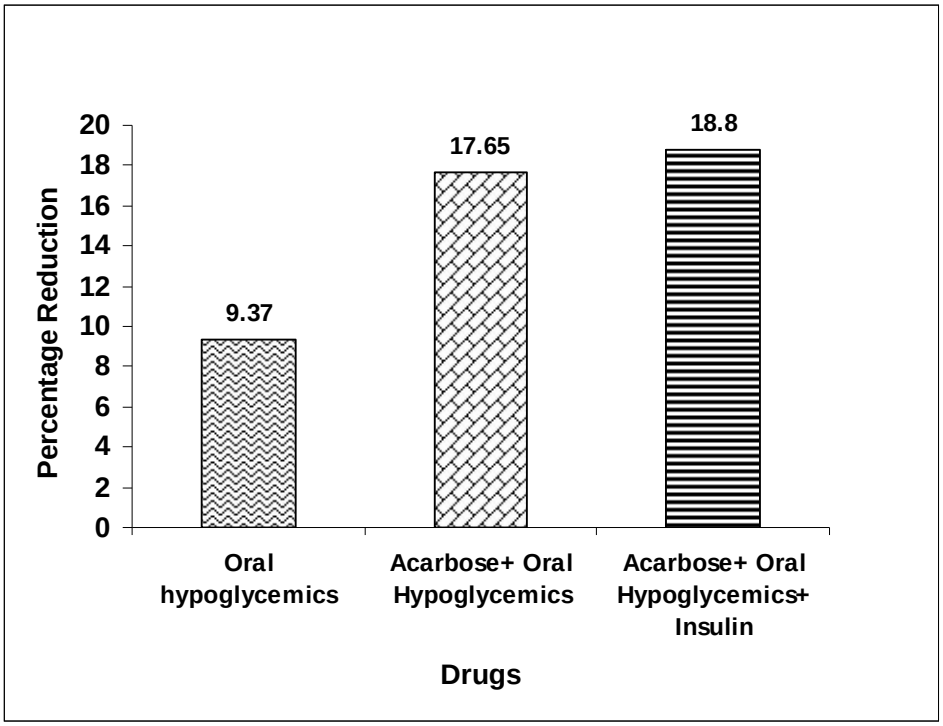


Table : 13 Percentage Reduction In PPBS in Acarbose treated group and in group without Acarbose

S.No	Drugs	Percentage Reduction
1	Oral Hypoglycemics	6.10
2	Acarbose + OralHypoglycemics	16.05
3	Acarbose + OralHypoglycemics + Insulin	16.82

Fig-13 Percentage Reduction in PPBS in each study group

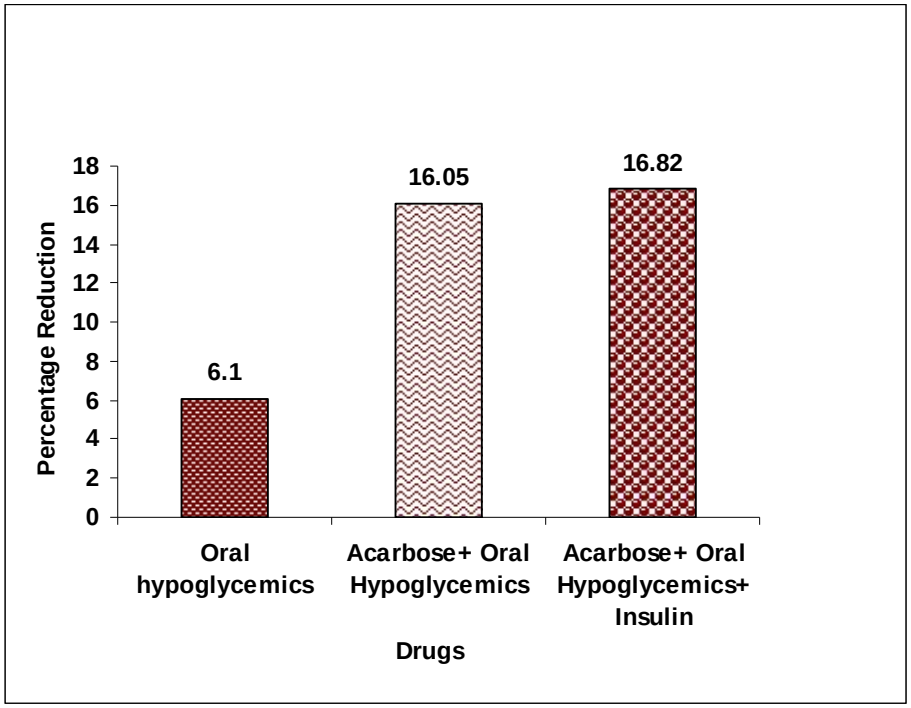


Table: 14 shows Percentage Reduction In HbA_{1C} in Acarbose treated group and in group without Acarbose

S.No	Drugs	Percentage Reduction
1	Oral Hypoglycemics	5.51
2	Acarbose + Oral Hypoglycemics	14.95
3	Acarbose + Oral Hypoglycemics + Insulin	17.92

Fig-14 Percentage Reduction in HbA_{1C} in each study group

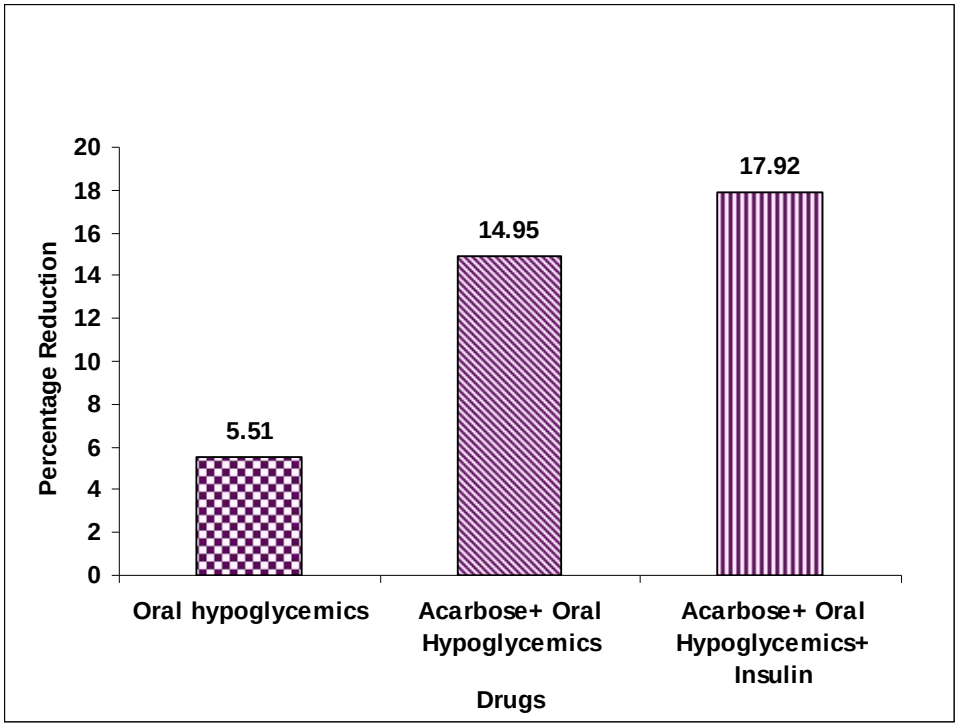


Table – 15: shows t test for the mean difference between baseline and review values of FBS in each group of patients

Drugs	Baseline FBS value (mean±SE)mg/dl	FBS at Review (mean±SE)mg/dl	FBS Reduction (mean ±SE)mg/dl	p value
Oral hypo glycemic drugs	169.96 ± 5.69	162.88± 5.87	7.08 ± 3.18	0.034*
Acarbose + Oral Hypoglycemics	171.75 ± 10.54	157.63± 38.65	14.12 ± 8.51	0.117
Acarbose + Oral Hypoglycemics + Insulin	173.47± 8.70	146.21±10.32	27.26± 6.57	0.0006**

Table – 16 shows 't' test for the mean difference between baseline and review values of PPBS in each group of Patients

Drugs	Baseline PPBS value (mean± SE) mg/dl	PPBS at review (mean± SE) mg/dl	PPBS Reduction (mean± SE) mg/dl	p value
Oral hypoglycemic drugs	264.73± 10.29	262.08± 9.18	2.65 ± 3.73	0.484
Acarbose + Oral hypoglycemics	263.87 ± 22.16	223.75 ± 16.86	40.12 ± 15.25	0.018*
Acarbose + Oral Hypoglycemics + Insulin	283.42± 16.34	241.58± 16.37	41.84±11.81	0.002**

Table-17: shows t test for the mean difference between baseline and review values of HbA_{1C} in each group of patients

Drugs	Baseline HbA1C value (mean± SE) mg/dl	HbA1C value at review (mean± SE) mg/dl	HbA1C Reduction (mean± SE) mg/dl	p value
Oral hypoglycemics	9.17 ± 0.24	9.12 ± 0.19	0.05 ± 0.11	0.692
Acarbose + Oral hypoglycemics	8.9 ± 0.80	7.76 ± 0.53	1.14 ± 0.37	0.0007*
Acarbose + Oral Hypoglycemics + Insulin	8.31 ± 0.49	7.07 ± 0.77	1.24 ± 0.48	0.043**

Table-18: shows t test for the FBS reduction in Obese and Non Obese patients

S.No	Category	Baseline FBS value (mean±SE)	FBS at review (mean± SE)	FBSReduction (mean± SE)	p value
1	Obese	177.59 ± 9.05	144.26 ± 8.29	33.33 ± 8.41	0.0005**
2	Non Obese	168.25±13.65	152.25±10.29	16 ± 12.59	0.244

Table-19: shows 't' test for the PPBS reduction in obese and non obese patients

S.No	Category	Baseline PPBS value (mean±SE)	PPBS at review (mean±SE)	PPBS Reduction (mean± SE)	p value
1	Obese	271.26± 15.67	225.74± 14.04	45.52 ± 11.58	0.0006**
2	Non Obese	284.88 ± 26.41	259.38 ± 17.50	25.5 ± 10.98	0.0532

Table -20: shows 't' test for HbA_{1C} Reduction in obese and non obese patients

S.No	Category	Baseline HbA1C value (mean± SE)	**HbA1Cat review (mean ± SE)**	**HbA1C reduction (mean± SE)**	p value
1	Obese	8.96±0.38	7.71± 0.39	1.25 ± 0.25	<o.ooo1**
2	Non Obese	8.07±0.85	7.41 ± 0.65	0.66 ± 0.30	0.03*

Results

RESULTS

The study was carried out at Kovai Medical Center and Hospital. A total of 74 Type II diabetic patients who visited the outpatient diabetic department of the hospital were included in our study. Out of which 40 patients were on Acarbose therapy and 34 patients were in another group taking oral hypoglycemic agents except Acarbose. In Acarbose treated group 35 patients came for review after a duration of 3 months and in the other group 26 patients came for review.

The demographic details among the subjects reveals that 42 (56.7) were males while 59 (43.2) were females {Table:1}. The mean age of the total population was 54.77 ± 9.60. The mean age of males and females were 55.14 ± 11.28 and 54.3 ± 10.6 respectively {Table:2}. From the past medical history hypertension was detected in 45 (60.14%) patients, Ischemic heart disease in 15 (20.06%), Hypercholestrolemia in 12 (16.2%), reactive depression in 7(9.4%), obesity in 24 (32.4%), renal impairment in 40 (29.7%) and foot ulcer in 58(43.2%).{Table:6} Distribution of patients evaluated as obese and non obese with respect to their body mass index was established as 72.9% and 27.02% respectively {Table: 3}

Family history of type II Diabetes mellitus was present in 48 (64.8%) and 26 (35.1%) had no history of diabetes mellitus. {Table:4}.Patients data were collected about their smoking habits and 67.5% were found to be smokers and 32.4% were found to be non smokers. Alcohol history of the study population was collected, out of this (59.4%) were found to be alcoholics and (40.5%) were non alcoholics.{Table:7}

Concerned with the duration of diabetes 17 (22.9%) had an experience of 0-5 years, 29 (39.1) had 6-10 years, 16 (21.6) had 11-15 years, 8 (10.8) had 16-20 years, and 4 (5.4) had 21-25 years of experience. {Table:5}. On considering the diet habits among the study population 56 (75.6%) patients were on diabetic diet and 18 (24.32%) were on non diabetic diet. {Table:8}. Age wise distribution of patients taking Acarbose among the study group were 6 (8%) in 30-39 years, 17 (23%) in 40-49 yrs, 22 (30%) in 50-59 years and 29 (39%) patients were in the age group of 60-69 years.

The different dose wise distribution of Acarbose among the study population were 25mg, 50mg and 100mg and the percentage of patients using different doses were 48.64%, 37.83% and 13.51%.{Table:9} Out of 40 patients on Acarbose therapy 35 came for review after duration of 3 months and 5 patients were considered as non respondents Based on their BMI they were classified as 27 (77.14%) as obese and 8 (22.8) as non obese. The percentage reduction of blood glucose level in each group of patients were done and it was found out that (81.4%) was reduced in obese patients and (75%) in non obese patients{Table:10}

The study population consisted of two groups where patients taking Acarbose was included in group I and patients taking other oral hypoglycemic agents were included in the group II. It was again divided into three groups where patients taking oral hypoglycemic agents except Acarbose was group I, Acarbose with oral hypoglycemic agents was group II, Acarbose with combination of oral hypoglycemic and Insulin considered as group III and the percentage reduction in FBS, PPBS and HbA1C produced in each group were calculated .

The percentage of patients taking other oral hypoglycemics were 26 (76.4%), Acarbose with oral hypoglycemics were 16 (45.7%), Insulin 12 (34.2%) and combination of oral hypoglycemics and Insulin were 7 (20%). {Table:11}

The mean difference between baseline and review values of FBS, PPBS and HbA1C in each group of study population ie obese and non obese were measured and the significant difference produced were compared by paired students t test. The baseline value of FBS in obese patients was found to be 177.59 ± 9.05 and for non obese patients it was found to be 168.25 ± 13.65. The review values in each group of patients was found to be respectively 144.26± 8.29 and 152.25 ± 10.29.The P value for obese patients were 0.0005 which is considered as highly significant and for non obese patients it was 0.244 which is not significant. {Table: 18}

The baseline value of PPBS in obese patients was found to be 271.26 ± 15.67 and in non obese patients the value was found to be 284.88 ± 26.41. The review values for both obese and non obese patients were found to be 284.88 ±26.41 and 259.38 ± 17.50. The P value for obese patients were 0.0006 which is highly significant and for non obese patients it was 0.0532 which is not significant. {Table:19}

The baseline value of HbA_{1C} in obese patients was found to be 8.96±0.38 and in non obese patients the value was 8.07±0.85. The review value in both these groups were found to be 7.71± 0.39 and 7.41 ± 0.65. The P value in case of obese patients were found to be <0.0001 which is considered as highly significant and for non obese patients it was 0.03 which is also significant. {Table:20}

Again the study population was divided into three groups where Acarbose was given in combination with other antidiabetic drugs such as oral hypoglycemics, Insulin and combination of oral hypoglycemics and Insulin. The mean difference in FBS, PPBS

and HbA_{1C} in these three groups were measured and the significant difference produced were compared by pared students t test.

The baseline value of FBS in these three study groups were found to be respectively 169.96 ± 5.69, 171.75 ± 10.54 and 173.47 ± 8.70. The review values of FBS in these three groups were found to be 162.88 ± 5.87, 157.63 ± 38.65 and 146.21 ±10.32. The P value for first group, oral hypoglycemic agents were found to be 0.034 which was significant, the second group ie combination of Acarbose and oral hypoglycemic agents were found to be 0.117 which is not significant. The P value for the third group where Acarbose was given in combination with oral hypoglycemics and Insulin was found to be 0.0006 which is highly significant. {Table:15}

The baseline value of PPBS in three group of patients were found to be 264.73 ± 10.29, 263.87 ± 22.16 and 283.42 ± 16.34. The review values in each group of patients were found to be 262.08± 9.18, 223.75 ± 16.86 and 241.58± 16.37. The p value for first group was 0.484 which was not significant. The p value for second and third group were found to be 0.018 and 0.002 which is highly significant.{Table: 16}
The baseline values of HbA1C in the three group of patients were found to be 9.17 ± 0.24, 8.9 ± 0.80 and 8.31 ± 0.49. The review values in each study group was found to be 9.12 ± 0.19, 7.76 ± 0.53 and 7.07 ±0.77. The p value for the first group was found to be 0.692 which was not significant and the p value for the other two groups were found to be 0.0007 and 0.043 which was considered to be highly significant. {Table:17}

Discussion

DISCUSSION

The prevalence of Diabetes mellitus is reported to be 6% of world's population in few studies[1] and age related prevalence was found to be 8.4% in men and 7.9% in women. The prevalence and incidence of type II diabetes is rising rapidly with Asia and Africa having the greatest potential increases.[8] Efficacy of α- glucosidase inhibitor Acarbose has been confirmed in more than 350 studies involving more than 30,000 patients. It was shown to be efficacious and have an excellent safety profile with minimal drug interactions. It is currently the only oral antidiabetes agent approved for the treatment of both prediabetes and Type II diabetes.[49] In our study the percentage of patients taking Acarbose was found to be higher in males (56.7%) than females (43.2%). The mean age distributions of our study population for male and female subjects were found to be 55.14 ±11.28 and 54.3 ± 10.6 respectively.

There is increased risk of hypertension in Diabetes mellitus patients, being compatible with our finding was 6% and treatment with Acarbose showed improved glycemic control in hypertensive diabetic patient. **P.Rosenbaum et al** have reported that half of all diabetic patients are hypertensive and 64% of patients showed a reduction in 24-hr systolic BP and 0.8% reduction in HbA_{1C} was obtained.[30]

Cardiovascular disease, a comorbid disease was found to be 20% and treatment with Acarbose significantly reduced the macrovascular complications with significant cardiovascular benefits. **Peter N Bavenholm** have shown that cardiovascular disease

accounts for upto 80% of death in patients with diabetes and intensive glucose control significantly reduce the macrovascular complications by 25%.[36]

Henrick Wagner et al have reported 48 of 62 type 2 diabetic patients patients (77.4%) as having cardiovascular disease in the study population.[38] We detected cardiovascular disease in thyroid disorders in 18.9% and renal disease in 29.7 % of our study population.

The study revealed that Acarbose was found to be a safe and tolerable drug and no serious adverse events could be linked to that drug but only few gastrointestinal symptoms were related to the drug. It caused flatulence in (20%) diarrhea in (11.4%) and (5.7%) patients reported of hypoglycemia**. Jean- Louis Chiasson et al** has found similar results in their study that Acarbose dose as large as 200mg had no toxic effect or serious adverse events and only gastrointestinal symptoms could be related. Compared with placebo, it was more frequently associated with flatulence (73.2%), diarrhea (43.6%) and abdominal cramps and discomfort was found to be 25%.[16]

The study revealed that Acarbose was more effective in obese Type II diabetic patients than non obese patients. The prevalence of obesity in this study was high. Obesity is a disorder and it results from a complex interplay of environmental and genetic factors which is associated with significant morbidity and mortality. It plays a major role in the development of the metabolic syndrome, which consists of insulin resistance, diabetes, hypertension, and dyslipoproteinemia.[7] In our study obese patients were found to be higher and showed a percentage reduction of 81.4% and 75% in non obese patients.

S.Halmi et al in their study also showed the same result. It has been found that Acarbose significantly improved the metabolic profile of overweight patients with

Type II diabetes who had inadequate glycemic control. The potential of Acarbose to delay the need for exogenous Insulin, in addition to producing statistically significant decrease in HbA1C, FBS and PPBS support its use for improving day to day metabolic control. Here Acarbose treated group had 0.9% decrease in HbA1C and it was associated with 25% reduction in the risk of microvascular endpoints.[59]

In our study it have been found that BMI did not showed a significant difference in obese and non obese patients before and after Acarbose treatment. It is usually calculated by dividing weight (in kilograms) by square height (in meters). It correlates significantly with body fat, morbidity, and mortality and can be calculated quickly and easily.[7] The total review patients including both obese and non obese showed significant difference. **Chien- Wen Chou et al** in their study showed the same results. Here obese patients change in BMI were considered not significant and non obese patients change in BMI showed a p value of ($p= 0.0579$).But the total patients had a significant decrease in body weight after treatment which showed a p value of <0.05 which is considered as highly significant. [12]

In our study it has been shown that obese patients showed significant reduction FBS, PPBS and HbA1C. (P value of 0.0005, 0.0006 and <0.0001). In case of non obese patients FBS and PPBS didn't showed a significant result but HbA1C showed significant difference. **Chein –Wen Chou et al** in their study suggested that both obese and non obese patients showed significant differences in FBS,PPBS and HbA1C.All the parameters in obese patients and non obese patients showed a significant P value.[12]

From the study which we have done it showed significant reduction in FBS, PPBS and HbA1C when Acarbose was combined with other antidiabetics. The study

population was divided into three groups where patients on oral hypoglycemic agents alone was considered as one group and patients taking combination of Acarbose with oral hypoglycemics was second group and the third group consist of both oral hypoglycemics and Insulin. Monotherapy using Acarbose was not seen in any of the patients. The p value for FBS in the first two groups were found to be not significant but in the third group it was found to be significant. The values of PPBS in the first group was 0.484. In the second and third group it was significant (p=0.018) and (p=002).. The p value of HbA_{1C} in the first group was 0.692 which was not significant and in the other two groups 0.0007 and 0.043 which were highly significant.

L.Saniorgio et al in their study revealed the significant reduction produced in blood glucose values when Acarbose was added to the current medications. Here the study population was divided into two groups. Group I consist of patients taking combination of Acarbose with oral hypoglycemics. Group II consist of patients undergoing treatment with Insulin alone or in combination with oral hypoglycemics. The P value of the three parameters in Group I were found to be <0.004, <0.0005 and <0.05.Similarly the P values in Group II was found to be <0.004, <0.0006 and <0.02. When Acarbose was stopped the blood glucose values increased.[28]

Boniface. J. Lin et al conducted a study to assess the efficacy of Acarbose in Asian patients. It concluded that Acarbose is generally efficacious in reducing HbA1c levels irrespective of which concomitant therapy such as diet, sulfonyl ureas or combination of antidiabetic drugs. It also states that PPBS were reduced significantly in Acarbose treated group. Thus it provides a useful tool in the reduction of macrovascular com plications development.[8]

Conclusion

CONCLUSION

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. Type II diabetes is a complex condition because there is a combination of insulin resistance together with impaired pancreatic beta cell function and thus leads to relative insulin deficiency. The different factors which may contribute to type II DM are greater longevity, obesity, unsatisfactory diet, sedentary life style and increasing urbanization. Acarbose is the first α glucosidase inhibitor that acts in the gastro intestinal tract and it has got wide margin of safety profile and low incidence of side effects.

It represents a new approach to the management of NIDDM thus modulating gastro intestinal carbohydrate metabolism to control post prandial hyperglycemia and to maximize the long term glycemic control. Our study was focused on evaluating the therapeutic efficacy and tolerability of Acarbose in Type II diabetic patients in a clinical practice setting in an Indian population. It was found that mainly obese patients with elevated blood glucose profile have reduced blood glucose value with Acarbose polytherapy. Thus it has been more effective in reducing the blood glucose profile in obese patients as compared to non obese patients .

The different doses of Acarbose which prescribed were 25mg, 50mg and 100mg. Patients on oral hypoglycemic agents showed significant reduction in FBS while patients on Acarbose therapy showed significant reduction in PPBS and HbA1C. No

systemic side effects were observed and only few gastrointestinal side effects such as abdominal flatulence and loose stools were reported.

From this study it has been concluded that Acarbose can be safely combined with other antidiabetic drugs such as oral hypoglycemic agents and Insulin. It was found to be safe and well tolerated due to its non systemic mode of action. It was also found that Acarbose in combination with oral hypoglycemics and Insulin was effective in reducing the PPBS and HbA1C than oral hypoglycemic agents alone used.

Our study is a short term study involving only a small number of study population. Hence in the future controlled long term studies involving large number of patients are still needed to be carried out to evaluate if the advantages of addition of Acarbose are persistent and whether it is possible to obtain a reduction in vascular complications and mortality.

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Annexure

DATA ENTRY FORM

SL NO:-	**Date of admission:-**
OP / IP No:-	**Age: .....Years Sex: Male/Female**
Name:-	**Ht:- Wt:-**
Address :-	**BMI:-**
Occupation:-_ _ _ _ _ _ _ _ _ **Family History:- Yes/ No**	**BP:- ..... mm Hg**
Duration Of Diabetes:- **Other Complications :-** **Diet:- Veg/ Non Veg**	
Social Habits: ☐ **Smoking** ☐ **Alcohol** ☐ **Pan/ Hans** ☐ **Tea/ Coffee**	
Chief Complaints _	**Examination** _
Past Medical History:-	**Past Medication History** ....

ALLERGY ☐ **YES** ☐ **NO**		
MONITORING PARAMETERS		
Parameters	Baseline	After Review
1) FBS 2) RBS 3) PPBS 4) HbA1C 5) BMI 6) BP 7) CHOLESTEROL 8) TRIGLYCERIDES 9) LDL 10) HDL		
CURRENTLY PRESCRIBED DRUGS AND DOSAGE		
Drugs	Dose	Frequency